Rheumatology Suggested Reading List

Compiled by Rebecca Sharim MD

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Rheumatoid Arthritis:

  - The results provide the first good evidence that specific cytokine blockade can be effective in human inflammatory disease and define a new direction for the treatment of rheumatoid arthritis.

  - As compared with oral methotrexate, subcutaneous etanercept acted more rapidly to decrease symptoms and slow joint damage in patients with early active rheumatoid arthritis.

  - Methotrexate may provide a substantial mortality benefit, likely by reducing cardiovascular risk.

  - In patients with active rheumatoid arthritis despite methotrexate treatment, a single course of two infusions of rituximab, alone or in combination with either cyclophosphamide or continued methotrexate, provided significant improvement in disease symptoms at both weeks 24 and 48.

- **TICORA** study: A strategy of intensive outpatient management of rheumatoid arthritis substantially improves disease activity, radiographic disease progression, physical function, and quality of life at no additional cost.


- **BeSt** trial – in early RA, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage at 1 year than did sequential monotherapy or step-up combination therapy


- Abatacept produced significant clinical and functional benefits in patients who had had an inadequate response to anti-TNF-α therapy.


- Risk of lymphoma is substantially increased in a subset of patients with RA, those with very severe disease. High inflammatory activity, rather than its treatment, is a major risk determinant.


- **OPTION** study: Tocilizumab could be an effective therapeutic approach in patients with moderate to severe active rheumatoid arthritis.
  o **COMET** trial: Both clinical remission and radiographic non-progression are achievable goals in patients with early severe rheumatoid arthritis within 1 year of combined treatment with etanercept plus methotrexate.

  o In patients with active rheumatoid arthritis, tofacitinib monotherapy was associated with reductions in signs and symptoms of rheumatoid arthritis and improvement in physical function

  o With respect to clinical benefit, triple therapy, with sulfasalazine and hydroxychloroquine added to methotrexate, was noninferior to etanercept plus methotrexate in patients with rheumatoid arthritis who had active disease despite methotrexate therapy.

**Gout:**

  o Colchicine prophylaxis during initiation of allopurinol for chronic gouty arthritis reduces the frequency and severity of acute flares, and reduces the likelihood of recurrent flares. Treating patients with colchicine during initiation of allopurinol therapy for 6 months is supported.


- At all doses studied, febuxostat more effectively lowered and maintained serum urate levels <6.0 mg/dl than did allopurinol (300 or 100 mg) or placebo in subjects with hyperuricemia and gout, including those with mild to moderately impaired renal function.

  - CONFIRMS trial: Urate-lowering efficacy of febuxostat 80 mg exceeded that of febuxostat 40 mg and allopurinol (300/200 mg), which were comparable. In subjects with mild/moderate renal impairment, both febuxostat doses were more efficacious than allopurinol and equally safe. At the doses tested, safety of febuxostat and allopurinol was comparable.

**Ankylosing spondylitis:**

  - SSZ at a dosage of 2,000 mg/day does not seem to be more effective than placebo in the treatment of AS patients with chronic, longstanding disease. SSZ is well tolerated and may be more effective than placebo in the treatment of AS patients with peripheral joint involvement. This effect is more pronounced in treatment of the peripheral arthritis in this subgroup of AS patients.

  - Treatment with infliximab is effective in patients with active ankylosing spondylitis

- **MEASURE:** Secukinumab at a subcutaneous dose of 150 mg, with either subcutaneous or intravenous loading, provided significant reductions in the signs and symptoms of ankylosing spondylitis at week 16. Secukinumab at a subcutaneous dose of 75 mg resulted in significant improvement only with a higher intravenous loading dose.

Psoriatic Arthritis:


- **PSUMMIT:** Ustekinumab significantly improved active psoriatic arthritis compared with placebo, and might offer an alternative therapeutic mechanism of action to approved biological treatments.


- **PALACE1:** Apremilast was effective in the treatment of psoriatic arthritis, improving signs and symptoms and physical function. Apremilast demonstrated an acceptable safety profile and was generally well tolerated.


- **FUTURE2:** Subcutaneous secukinumab 300 mg and 150 mg improved the signs and symptoms of psoriatic arthritis, suggesting that secukinumab is a potential future treatment option for patients with this disorder.
Scleroderma:

  - This describes the first successful treatment of SRC with ACE inhibitors.
  - Renal crisis can be effectively managed when hypertension is aggressively controlled with ACE inhibitors. Patients should continue taking ACE inhibitors even after beginning dialysis in hopes of discontinuing dialysis.
  - **Scleroderma Lung Study:** One year of oral cyclophosphamide in patients with symptomatic scleroderma-related interstitial lung disease had a significant but modest beneficial effect on lung function, dyspnea, thickening of the skin, and the health-related quality of life. The effects on lung function were maintained through the 24 months of the study.
  - **Scleroderma Lung Study II:** Treatment of scleroderma-related interstitial lung disease with mycophenolate mofetil for 2 years or cyclophosphamide for 1 year both resulted in significant improvements in prespecified measures of lung function over the 2 year course of the study. Although mycophenolate mofetil was better tolerated and associated with less toxicity, the hypothesis that it would have greater efficacy at 24 months than cyclophosphamide was not confirmed. These findings support the potential
clinical effectiveness of both cyclophosphamide and mycophenolate mofetil for progressive scleroderma-related interstitial lung disease, and the present preference for mycophenolate mofetil because of its better tolerability and toxicity profile.

Systemic Lupus Erythematosus:

  - Patients with quiescent SLE who are taking hydroxychloroquine are less likely to have a clinic flare-up if they are maintained on the drug.
  - An extended course of pulse cyclophosphamide is more effective than 6 months of pulse methylprednisolone in preserving renal function in patients with severe lupus nephritis. Addition of a quarterly maintenance regimen to monthly pulse cyclophosphamide reduces the rate of exacerbations.
  - For patients with proliferative lupus nephritis, short-term therapy with intravenous cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine appears to be more efficacious and safer than long-term therapy with intravenous cyclophosphamide.
SELENA: Hormone replacement therapy given for 1 year does not significantly increase the risk for severe flare but does increase the risk for mild to moderate flares in menopausal women with SLE.

  - In this 24-week trial, mycophenolate mofetil was more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis and had a more favorable safety profile.

  - LUMINA: Hydroxychloroquine, which overall is well tolerated by patients with SLE, has a protective effect on survival which is evident even after taking into consideration the factors associated with treatment decisions. This information is of importance to all clinicians involved in the care of patients with SLE.

  - EXPLORER: Enrolled patients with moderately-to-severely active SLE and used aggressive background treatment and sensitive cutoffs for nonresponse. No differences were noted between placebo and rituximab in the primary and secondary end points. Further evaluation of patient subsets, biomarkers, and exploratory outcome models may improve the design of future SLE clinical trials.

- **MAINTAIN** trial: Tested whether MMF was superior to azathioprine for maintenance therapy. Fewer renal flares were observed in patients receiving MMF but the difference did not reach statistical significance.

  - Belimumab plus standard therapy significantly improved SRI response rate, reduced SLE disease activity and severe flares, and was generally well tolerated in SLE

  - **ALMS** trial: Mycophenolate mofetil was superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who had a response to induction therapy

  - **LUNAR** trial: Although rituximab therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels, it did not improve clinical outcomes after 1 year of treatment. The combination of rituximab with MMF and corticosteroids did not result in any new or unexpected safety signals.

**Myositis:**

- High dose IVIG is a safe and effective treatment for refractory dermatomyositis.

  - Although there were no significant differences in the two treatment arms for the primary and secondary endpoints, 83% of refractory adult and juvenile myositis patients met the DOI. The role of B cell depleting therapies in myositis warrants further study with consideration for a different trial design.

**Vasculitis:**

  - This study provides a prospective experience with Wegener's granulomatosis and shows that long-term remissions can be induced and maintained in an extremely high number of patients by the combination of daily cyclophosphamide and alternate-day prednisone therapy.

  - In patients with generalized vasculitis, the withdrawal of cyclophosphamide and the substitution of azathioprine after remission did not increase the rate of relapse. Thus, the duration of exposure to cyclophosphamide may be safely reduced.

- **CYCLOPS** study: The pulse cyclophosphamide regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen at a reduced cumulative cyclophosphamide dose and caused fewer cases of leukopenia.

  - **RAVE** trial: Rituximab therapy was not inferior to daily cyclophosphamide treatment for induction of remission in severe ANCA-associated vasculitis and may be superior in relapsing disease.

  - **RITUXVAS:** A rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe ANCA-associated vasculitis. Sustained-remission rates were high in both groups, and the rituximab-based regimen was not associated with reductions in early severe adverse events.

  - More patients with ANCA-associated vasculitides had sustained remission at month 28 with rituximab than with azathioprine.

**Sjogren's:**

  - **JOQUER:** Among patients with primary Sjögren syndrome, the use of hydroxychloroquine compared with placebo did not improve symptoms during 24 weeks of treatment. Further studies are needed to evaluate longer-term outcomes.
Osteoporosis:

  o **FOSIT** study: For postmenopausal women with low bone mass, alendronate is well tolerated and produces significant, progressive increases in BMD at the lumbar spine and hip in addition to significant reduction in the risk of nonvertebral fracture.

  o **FLEX**: Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.

  o Denosumab treatment led to significantly greater reduction of bone turnover markers compared with alendronate therapy. Adverse events and laboratory values were similar for denosumab- and alendronate-treated subjects. Denosumab showed significantly larger gains in BMD and greater reduction in bone turnover markers compared with alendronate. The overall safety profile was similar for both treatments.

- Subjects with glucocorticoid-induced OP treated with teriparatide for 36 months had greater increases in BMD and fewer new vertebral fractures than subjects treated with alendronate.


- **DATA** study: Combined teriparatide and denosumab increased BMD more than either agent alone and more than has been reported with approved therapies. Combination treatment might, therefore, be useful to treat patients at high risk of fracture.

**Systemic JIA:**


- **ANAJIS**: Anakinra treatment is effective in SJIA, at least in the short term. It is associated with normalisation of blood gene expression profiles in clinical responders and induces a de novo IFN signature.

**Giant Cell Arteritis:**

Our findings show, for the first time in a trial setting, the efficacy of tocilizumab in the induction and maintenance of remission in patients with giant cell arteritis.